Claims 14-16, 21 and 38-40 have been rejected under 35 U.S.C. 112, first and second paragraph. In order to further prosecution, without conceding to the correctness of the rejection, the pending claims have been amended to recite a "tumor cell specific TRE". Applicants have provided multiple specific examples of tumor cell specific TREs, including TREs specific to prostate cells (a prostate-specific TRE or PSA-TRE, a glandular kallikrein-1 TRE or hKLK2-TRE, and a probasin TRE or PB-TRE) (page 34, line 1 through page 35, line 15); and cancer specific TREs, such as an α-fetoprotein (AFP) (liver cancer), a mucin-like glycoprotein DF3 (MUC1) (breast carcinoma), a carcinoembryonic antigen (CEA) (colorectal, gastric, pancreatic, breast, and lung cancers), a plasminogen activator urokinase (uPA) and its receptor gene (breast, colon, and liver cancers), a HER-2/neu (c-erbB2/neu) (breast, ovarian, stomach, and lung cancers) (page 35, line 18 through page 40, line 18).

The present application provides guidelines that direct one of skill in the art in selection of a TRE, in addition to the specific examples described above. "By transcriptional activation, it is intended that transcription is increased in the target cell above the levels in a control cell (e.g., a that cell when not exhibiting a requisite physiological state (generally a normal physiological state) by at least about 2 fold, preferably at least about 5 fold, preferably at least about 10 fold, more preferably at least about 20 fold, more preferably at least about 50 fold, more preferably at least about 100 fold, more preferably at least about 200 fold, even more preferably at least about 400 fold to about 500 fold, even more preferably at least about 1000 fold. The normal levels are generally the level of activity (if any) in a cell as tested under conditions that activate the TRE, or the level of activity (if any) of a reporter construct lacking such a TRE as measured in a cell exhibiting the requisite physiological condition."

Applicants respectfully submit that in the art, as practiced at the time the present application was filed, the use of regulatory elements in expression systems was exceedingly well known, and as evidenced by the numerous examples provided by Applicants, a number of tumor cell specific transcriptional regulatory elements were publicly available. In view of the methods known in the art, and disclosure of the exemplary constructs, the specification is fully sufficient to describe the claimed constructs in clear and concise terms, and shows possession of the same.

The Patent Office guidelines state that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Applicants note that recitation in a claim of a generic element, (for example tumor specific TREs in general, rather than, say, a specific promoter and enhancer combination), does not require that the specification list each and every promoter that might be used with the invention. Rather, one may rely on the many promoters known in the art to be useful in initiation transcription of a proximal gene. Indeed, as set forth in the MPEP: a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc*., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In view of the specific examples and general guidance provided by Applicants, one of skill in the art could readily determine a suitable tumor cell specific TRE for use in the compositions and methods of the present invention. Withdrawal of the rejection is requested.

Claims 1, 8, 24, 26 and 40 have been rejected under 35 U.S.C. 112, second paragraph as indefinite in the recitation of a "hypoxia responsive element". Applicants respectfully submit that the term clearly informs one of skill in the art of the metes and bounds of the claimed invention, and meets the requirements of 35 U.S.C. 112.

The present specification describes the transcriptional complex HIF-1, which is induced under hypoxic conditions, and which then interacts with binding sites to regulate transcription of genes, including vascular endothelial growth factor, and glycolytic enzymes, including enolase-1 (page 22, line 24 through page 23, line 4).

It was known in the art at the time of filing that the binding site for HIF-1 is a 32-base pair hypoxia-responsive element, which contains two hypoxia-inducible factor-1 (HIF-1) binding sites (HBSs). Jiang *et al.* (cited on page 49, lines 14-16), discusses increased expression in hypoxic cells is mediated in part by binding of HIF-1 to cis-acting HREs located primarily in the 5' regions of these genes (p. 5328). The paper goes on to describe (p. 5331) the use of a plasmid construct which contained a 68 bp HRE from the ENO1 gene 5' flanking region. It can be seen in Jiang *et al.* that an Eno1 HRE has the sequence starting with a 5' AGGGCCGGACGTGGGGCCCC, followed by an undefined 28 nucleotides, then the 3' sequence. Jiang et al. cite an earlier publication (Semenza et al. (1996) J. Biol. Chem 271:32529-32537) for further details about this HRE. The Semenza *et al.* paper discloses the sequence of a functional HIF-1 binding site in an HRE as "ACGCTGAGTGCGTGCGGGACTCGGAGTACGTGACGGAGCCCC". Hence, one of skill in the art would readily be able to determine the metes and bounds of the claimed invention, as an HRE is a well-defined binding site. Withdrawal of the rejection is requested.

Claims 1, 8, 14-16, 21, 25, 26 and 32-46 have been rejected under 35 U.S.C. 103 as being unpatentable over either one of Henderson *et al.* (WO97/01358); Hallenbeck *et al.* (WO96/17053), Walther *et al.* (Mol. Biotechnol. 6:267-286); Dachs *et al.* (Nat. Med. 3:515-520); Dachs *et al.* (Oncol. Res. 9:313-325); Advani *et al.* (Semin. Oncol. 24:633-638), and Parr *et al.* (Nat. Med. 3:1145-1149). Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references.

Neither Henderson (WO 97/01358) nor Hallenbeck (WO 96/17053) teach nor render obvious replication-competent adenovirus vectors comprising a hypoxia responsive element (HRE) (claims 1,8, 14-16, 21, 24-26, 32-34); or replication-competent adenovirus vectors comprising an E2F-1 transcriptional regulatory element (TRE) (claims 35-46), as encompassed by the present claims. On page 25 of the 9/14/01 Office Action (paper 16), the Examiner acknowledges that neither Henderson nor Hallenbeck teach an adenovirus vector comprising a hypoxia responsive element (HRE) or a cell cycle-specific element is from the E2F-1 gene (claims 9 and 12, as filed, respectively), as encompassed by the present claims.

As previously discussed, Walther *et al.*, 1996, is a gene therapy review directed to targeted vectors for gene therapy of cancer. On page 26 of the 9/14/01 Office Action (paper 16), the Examiner acknowledges that Walther *et al.* does not teach or suggest "hypoxia-inducible response elements" or "cell cycle-specific elements (i.e. E2F), as encompassed by the present claims.

Dachs *et al.*, Nature Medicine, 1997 teaches targeted gene therapy for treating cancer patients where the hypoxic environment of a tumor facilitates heterologous gene expression. The Examiner acknowledges that Dachs *et al.* does not teach or suggest replication competent adenovirus vectors comprising cell-status TREs, as encompassed by the present claims.

Dachs *et al.*, Oncology Research, 1997, is a review directed to vectors for targeted delivery of therapeutic genes for gene therapy of caner, which recites numerous cancer-associated regulatory elements. Dachs *et al.* does not teach or suggest vectors for cell specific adenoviral gene expression.

Advani *et al.*, 1997 is cited as teaching cell status TREs comprising radiation-inducible promoters. The Examiner acknowledges that Advani *et al.* does not teach or suggest the use of hypoxia inducible TRE elements, as encompassed by the present claims.

Parr *et al.*, 1997 is cited as disclosing adenoviral vectors for gene therapy, which comprise a transgene operably linked to the E2F-1 promoter. Parr *et al.*, does not teach or suggest replication competent adenovirus vectors comprising an HRE, as encompassed by the present claims.

The Walther *et al.* reference, the two Dachs *et al.* references, the Advani *et al.* reference and the Parr *et al.* reference, describe vectors for targeted gene therapy which by their nature are replication defective. Accordingly, one of skill in the art would not be motivated to combine such gene therapy references with Henderson (WO 97/01358) and Hallenbeck (WO 96/17053), cited as teaching conditionally replication competent adenovirus vectors.

Furthermore, the Examiner has acknowledged that none of Henderson, Hallenbeck (WO 96/17053) Walther *et al.*, 1996, or Dachs *et al.* Nature Medicine, 1997, teach or suggest "hypoxia-inducible response elements" or "cell cycle-specific elements (i.e. E2F), as encompassed by the present claims.

In view of the above remarks, withdrawal of the rejection is requested.

Claims 14-16 and 21 have been provisionally rejected under the judicially created doctrine of obviousness type double patenting as unpatentable over claims 1-4, 8 and 32 of co-pending application no. 09/151,376. The Office Action states that the rejected claims fully embrace Claims 1-4, 8 and 32 of the co-pending application.

Applicants respectfully submit that the rejected claims are not made obvious by the cited co-pending application. The rejected claims specifically recite the inclusion of a composite regulatory element comprising a HRE and a tumor cell-specific transcriptional regulatory element. The co-pending claims fail to suggest a composite TRE specifically comprising an HRE. Withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-014.

Respectfully submitted,

Date: August 22, 2002

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APPENDIX
VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Page 9, lines 5-15, replace with the following rewritten description:

Figure 1 is a schematic representation of adenovirus vector CN796, in which the E1A gene is under transcriptional control of an HRE and a PSA-TRE, as described in Example 1.

[Figure 2 shows the nucleotide sequence of an HRE from the 5' flanking region of a rat enolase-1 gene (SEQ ID NO:1).]

Figure [3] 2 shows the nucleotide sequence of the 5' flanking region of a human E2F1 gene (SEQ ID NO:[2] 1). The asterisk indicates the transcription start site.

Figure [4] 3 depicts a nucleotide sequence of a prostate-specific antigen TRE.

Figure [5] 4 depicts a nucleotide sequence of a carcinoembryonic antigen TRE.

Figure [6] 5 depicts a nucleotide sequence of a human glandular kallikrein TRE.

Figure [7] 6 depicts a nucleotide sequence of a mucin TRE.

Figure [8] 7 depicts a nucleotide sequence of a rat probasin TRE.

Figure [9] 8 depicts a nucleotide sequence and translated amino acid sequence of an adenovirus death protein.

Replace the Sequence Listing with the attached substitute Sequence Listing.

14. (amended) The adenovirus vector of claim 1, wherein said adenovirus gene essential for replication is operably linked to a composite regulatory element comprising said HRE and a [cell-type specific] tumor cell-specific transcriptional regulatory element (TRE).

15. (amended) The adenovirus vector of claim 14, wherein said [cell-type specific] tumor cell-specific TRE comprises a promoter.

16. (amended) The adenovirus vector of claim 14, wherein said [cell-type specific] tumor cell-specific TRE comprises an enhancer.

21. (amended) The adenovirus vector of claim 14, wherein said [cell-type specific] tumor cell-specific TRE comprises a prostate specific promoter and enhancer.

34. (amended) The adenovirus vector of claim 14, wherein said [cell-type specific] tumor cell-specific transcriptional regulatory element (TRE) is selected from the group consisting of a prostate-specific TRE (PSA-TRE), a glandular kallikrein-1 TRE (*hKLK2*-TRE), a probasin TRE (*PB*-TRE), an α-fetoprotein TRE (AFP TRE) and a carcinoembryonic antigen TRE (CEA TRE).

40. (amended) The adenovirus vector of Claim 35, wherein said adenovirus gene essential for replication is operably linked to a composite regulatory element comprising said E2F-1 transcriptional regulatory element (TRE) and a tumor cell-specific transcriptional regulatory element (TRE).

41. (amended) The adenovirus vector of claim 40, wherein said [cell-type specific] tumor cell-specific transcriptional regulatory element (TRE) is selected from the group consisting of a prostate-specific TRE (PSA-TRE), a glandular kallikrein-1 TRE (*hKLK2*-TRE), a probasin TRE (*PB*-TRE), an α-fetoprotein TRE (AFP TRE) and a carcinoembryonic antigen TRE (CEA TRE).